TUBERCULOSIS PHARMACOTHERAPY

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Objectives

- Identify the mechanism of action and adverse effects of the commonly used anti-tuberculosis agents
- Given a patient being treated for tuberculosis:
  - Identify significant drug interactions and the appropriate action which should be taken
  - Screen for the common adverse effects and determine whether they require discontinuation of therapy.

Case

HS is a 45 year old man just admitted to the hospital from the homeless shelter with a 2 week history of cough with bloody sputum and significant weight loss over the past few months. His sputum was positive for acid fast bacilli and his positive chest X-ray with cavitary lesions leads to a diagnosis of tuberculosis.

First Line anti-tuberculosis agents

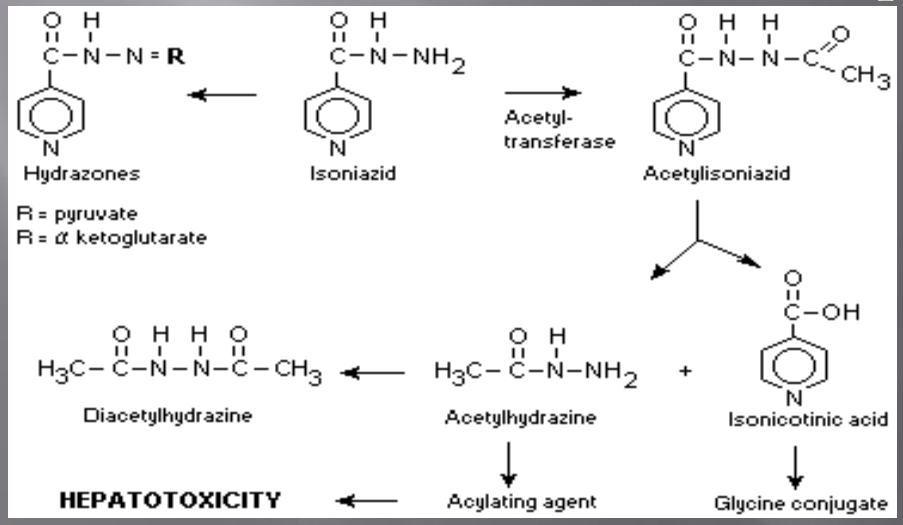
- Always used in combination for treatment
- Overlapping toxicities
- Many drug interactions

Isoniazid

- Probably the most effective agent against Tb
- MOA – inhibits production of mycolic acid, an essential component of Tb cell wall
- Very lipophilic, excellent penetration into most tissues.
- Metabolized primarily by acetylation which has a genetic polymorphism. About 50% are fast acetylators.
- INH has very few drug interactions.

Isoniazid

- Adverse Effects
  - Neurotoxicity
    - Must give Vitamin B6 (pyridoxine) 25-50mg/day
  - Hepatotoxicity
    - Rifampin increases isoniazid toxicity through induction of metabolism to a hepatotoxic metabolite (hydrazine)



http://www.inchem.org/documents/pims/pharm/pim288_2.gif

Rifampin

- Second most effective agent
- MOA – RNA polymerase inhibition
- Drug interactions
  - Induces microsomal liver enzymes
  - Primarily CYP3A4 but induces broadly
  - All drugs should be evaluated for interactions
  - Examples
    - Atorvastatin
    - Warfarin

Rifampin

- Adverse effects
  - Hepatotoxicity
  - Body Fluid discoloration
  - Nausea/Vomiting
- Particularly prone to resistance

Rifabutin

- NOT FDA Approved for treatment of Tb!!!!
- Very similar to Rifampin but less significant drug interactions
- Always used in place of rifampin in HIV patients receiving protease inhibitors
- Appears slightly less efficacious than rifampin.

Rifapentene

- Very similar to rifampin in most respects
- Less drug interactions than rifampin but less well studied with regard to interactions compared to rifabutin
- Longest half life of all the rifamycins
- Recent data

Pyrazinamide

- No activity as the parent compound – activated inside the macrophages at pH<5.5
- MOA – unknown
- Adverse effects
  - Hepatotoxicity (probably most of the first line anti-Tb agents)
  - Increases uric acid (watch in gout)

Ethambutol

- Least effective of first line drugs but increases activity of other agents
- MOA – Interferes with mycobacterial RNA synthesis
- Requires renal adjustment in severe dysfunction
- Adverse Effects
  - Hepatotoxicity
  - Optic neuritis (visual disturbances)

Questions to consider

- How would you respond to the development of the following toxicities?
  - Nausea and vomiting
  - Hepatotoxicity
  - Neurotoxicity (peripheral? Optic?)
  - Joint pain
  - Blood in the urine

Second – Line Drugs

- Generally reserved for toxicity or resistance
- Uniformly less active than first line drugs (or more toxic)
- Often the data is less robust

Aminoglycosides

- Aminoglycosides
  - Activity
    - Streptomycin>Amikacin=Kanamycin>
    Capreomycin
  - FDA indicated?
    - Yes: Streptomycin and Capreomycin
    - No: Amikacin and Kanamycin
  - Mechanism of action
    - Binds to the 30S portion of the ribosome – inhibits protein synthesis

Aminoglycosides

- Adverse Effects
  - Little to no hepatotoxicity
  - Ototoxicity
  - Nephrotoxicity
  - Electrolyte abnormalities
- Drug interaction limited to additive toxicities

Fluoroquinolones

- NONE are FDA Approved!!!!
- Fluoroquinolones
  - Activity
    - Moxi>Gati>Levo>Cipro
    - Do not use ciprofloxacin
    - Levofloxacin probably has the best clinical data
  - Well tolerated but not much clinical data although more is published each year
  - Rapidly becoming the most important second line agents.

Cycloserine

- Probably the best activity of the second line drugs
- Numerous, significant adverse effects
  - Hepatotoxicity
  - Electrolyte abnormalities
  - Seizures
  - Arrhythmias
  - Psychosis
  - Many others

2nd Line Drugs Continued

- Ethionamide – not FDA approved!!!!
  - Poorly tolerated (GI effects), neurotoxicity necessitating B6 supplementation
- p-aminosalicylic acid (PAS)
  - Fairly poor activity but generally well tolerated
  - Requires adjustment in renal dysfunction
- Linezolid – not FDA approved!!!
  - Anti-ribosomal – protein synthesis inhibitor
  - Excellent in-vitro activity
  - Clinical data unconvincing

Investigational Drugs

(Of course none of these are approved!!)

- Second generation oxazolidinones
- SQ109 – second generation ethane diamine
- Bedaquiline – diarylquinolones
- Nitroimidazoles
  - Delamanid

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Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

Considerations

A patient with XDR Tb is currently on:

Pyrazinamide, ethambutol, moxifloxacin, cycloserine, p-aminosalicylic acid and streptomycin.

What action would you take for the following adverse effects?

Visual disturbances

Low potassium

Increasing SCr

Increasing AST/ALT

Questions